Immunological three-way chat

Previous reports have implicated polymorphonuclear leukocytes (PMNs) in the immune response to *Candidas albicans* at the oral mucosa. Subsequent investigation revealed that mammalian Toll-like receptor 4 (TLR4), which serves as a pathogen pattern recognition receptor, is essential in the complex cross-talk among pathogen, immune system, and epithelia. In the presence of both *C. albicans* and PMNs, TLR4 mRNA and protein expression were upregulated in oral epithelium. This upregulation was tightly correlated with protection of the epithelium from cell damage. Blockade of TLR4 with specific antibodies or knockdown of TLR4 using RNAi restored a virulent phenotype, supporting the critical role of this receptor in orchestrating the potent immune response to microbial infection. Although direct contact between PMNs and epithelia is prevented, *C. albicans* appears to stimulate epithelial cell secretion of cytokines, including interleukin-8 and granulocyte–macrophage colony-stimulating factor, which then likely recruit PMNs to the site of infection and activate a cascade of events via TLR4. (*J Clin Invest* 117:3664–72, 2007)

Tumor cell evasion

Based on evidence that transplant organ recipients treated with T-cell immunosuppressive agents have a higher incidence of skin cancer, Pivarcsi and colleagues investigated mechanisms of tumor immune escape by transformed cells. Human skin tumors apparently downregulate expression of the keratinocyte-specific homeostatic chemokine CCL27. Activation of the Ras oncogene suppressed expression of CCL27 in keratinocytes. Recombinant epidermal growth factor (EGF) similarly decreased CCL27 expression, whereas inhibition of the EGF receptor with erlotinib, a small-molecule inhibitor, increased CCL27 protein expression *in vitro* and *in vivo*. This factor, which is downstream of Ras signaling, seemingly regulates the expression of CCL27. In a mouse model, CCL27-neutralizing antibodies enhanced tumor growth via inhibition of leukocytes at the tumor site. Thus, these results describe a novel mechanism used by tumors to evade immune surveillance and offer new possibilities for the development of antitumor immunotherapies. (*Proc Natl Acad Sci USA* 104:19055–60, 2007)

Negative effects of inflammation

During tissue repair, inflammatory cells are recruited to wound sites in order to defend against potential pathogens; however, these players can provoke a fibrotic response and contribute to scarring and related pathologies. Microarray studies demonstrated that osteopontin (OPN) is expressed in wound granulation tissue fibroblasts concurrently with wound inflammation. When Mori and colleagues downregulated OPN expression using antisense oligodeoxynucleotides in mouse skin wounds, the rate and quality of the wound repair were increased. In addition, downregulation of OPN altered collagen organization and decreased neutrophil and macrophage recruitment to wound sites. Increased vessel invasion was also noted. OPN, therefore, contributes to fibrosis via a variety of mechanisms, including stimulating the inflammatory response, altering matrix factors, and affecting angiogenesis. These findings illuminate potential targets for developing treatment of wounds and fibrosis. (*J Exp Med* 205:43–51, 2008)

Contribution to itch

The common skin disorder primary localized cutaneous amyloidosis (PLCA) presents with severe itching, a symptom that is not very well understood at the molecular level. The genetic locus, but not the affected gene, of this autosomal-dominant disease has previously been identified. Genetic mapping and subsequent candidate gene sequencing of DNA from a large Brazilian family with familial PLCA cases revealed a missense mutation in the oncostatin M receptor β (OSMRβ) gene in all affected patients. Further analysis of two other families confirmed mutations in this gene in affected patients. The mutations occurred in the extracellular fibronectin type III–like domains, which were previously implicated in receptor function and signaling transduction. Interestingly, stimulation of PLCA-cultured keratinocytes with appropriate ligands (OSM or interleukin-31) reduced phosphorylation of downstream signaling molecules with antiapoptotic effects (pSTATs, pERK, and pAkt). Thus, OSMRβ signaling may contribute to increased downstream apoptosis and to the itching phenotype in PLCA, although the mechanism of action is not yet clear. (*Am J Hum Genet* 82:73–80, 2008)

Human fibroblasts made pluripotent

Yamanaka's group previously generated induced pluripotent stem (iPS) cells from mouse somatic cells. This group recently described the successful generation of iPS cells from human dermal fibroblasts by transduction of the same four transcription factors: Oct3/4, Sox2, Klf 4, and c-*myc*. These cells were remarkably similar to human embryonic stem (ES) cells with respect to morphology, proliferation, global gene expression patterns, epigenetic modification of promoters of ES cell-specific genes, and growth. Under various differentiation media conditions, these human iPS cells differentiated into all three germ layers as well as into neural cells and cardiac myocytes. Formation of teratomas in immunodeficient mice demonstrated the pluripotent nature of these iPS cells as endodermal, mesodermal, and ectodermal tissues were identified. These findings are particularly promising for the generation of patient-specific therapies, as well as for drug discovery and toxicity testing; however, further research into the mechanism of induction of this pluripotency and into the differences between human iPS and human ES cells is essential. (*Cell* 131:1–12, 2007)

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